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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,163	11/17/2003	Ricardo Mayo-Alvarez	5009-1	3896

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 03/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,163	MAYO-ALVAREZ ET AL.	
	Examiner	Art Unit	
	Michele Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-24 and 26-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-4,6-24 and 26-40* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on January 3, 2005. Further acknowledgment is made of Applicant's cancellation of Claims 5 and 25.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 6-24 and 26-40 are under examination.

Response to Amendment

Claim Rejections - 35 USC § 102

Claims 1, 2 and 10 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by LaHann (A). Applicant's arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant argues that the amendment to the claims overcomes the teachings of LaHann because the claims do not recite codeine. However, this is not persuasive because LaHann teaches a pharmaceutical composition comprising proproxyphene (an analgesic), N-vanillyl-1-E-octadecenamide (a non-opioid analgesic, and methylcellulose (a stool softener) in the form of an oral solution, in Column 8, lines 50-68.

The reference anticipates the claimed subject matter.

Claims 1, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Merrill et al. (E).

Merrill teaches a tablet comprising: (a) either fentanyl, meperidine, methadone, propoxyphene or pentazocine (an analgesic); and, (b) carboxymethyl cellulose (a stool softener), wherein the analgesic is delivered at a therapeutically effective dose at a controlled rate over a sustained period of time up to 28 hours. See patent Claim 4; Column 2, lines 1-21; and, Column 11, lines 37-59.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1, 8-12, 16-19, 21, 28-30, 33 and 37-39 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V). The rejection stands for the reasons set forth in the previous office action and set forth below.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant argues the combination of an opioid and docusate in a single solid dosage form would not have been obvious to one of ordinary skill in the art as a mere matter of judicious choice of ingredients, despite the fact that Lazarus teaches that the simultaneous administration of sennosides, docusate and morphine to patients in need of analgesia reduces the frequency of constipation in patients. Applicant further argues that the morphine dosage range in relation to the docusate dosage range that was administered to the study patients taught by Lazarus represents a non-linear increase in the dosage of docusate and opioid amongst the patients. Thus, Applicant concludes, "But this non-linear increase in docusate dosage, or even decrease in docusate dosage, with a corresponding increase in morphine dosage would not have been possible using the single solid dosage form claimed in the instant application that would require a doubling of the docusate dose with every doubling of the morphine dosage." Applicant's further argues that one of skill in the art would not have been motivated to combine morphine (or an equivalent opioid) with docusate in a single form "because this ability to separately titrate the docusate dosage independent of the morphine dosage, noted to be so effective by Lazarus, would not have been possible with such a single dosage form." Finally, Applicant argues that Lazarus teaches away from the claimed invention based on the idea that "the titration of the opioid dose separate from the dose of the laxative and specifically will not allow doubling or quadrupling of the opioid dose without doubling of the dose of the laxative(s) contrary to the teachings of Lazarus." However,

Applicant's arguments are neither persuasive nor commensurate in scope to the limitations of the claimed invention because, as drafted, the claims are directed to methods of preventing constipation during analgesic use comprising administration of a pharmaceutical composition comprising a claim-designated stool softener(s), and combinations thereof with, a claim-designated analgesic(s) in a single oral dosage form, and combinations thereof, wherein the stool softener is from about 25 mg to about 200 mg of docusate; and wherein the stool softener is from about 50 mg to 100 mg of docusate. Nowhere in the claims, as drafted, does Applicant direct either the instantly claimed methods or instantly claimed single dose form pharmaceutical compositions to inventions encompassing limitations wherein the administration of the claim-designated pharmaceutical compositions require administration of a pharmaceutical composition wherein the increase of the dosage range of the stool softener, namely docusate, corresponds to a linear increase in the increase of the dosage range of the analgesic comprising the claim-designated pharmaceutical composition which is used to provide a beneficial amelioration of constipation during analgesic use. In fact, the claims only require that the pharmaceutical composition comprise claim-designated dose amounts of a stool softener without regard to any amount of the analgesic component of the claim-designated pharmaceutical composition, as mentioned above. In an attempt to further support Applicant's premise that Lazarus teaches away from the claimed invention, Applicant points to Figure I. However, it appears that Applicant has misconstrued the findings represented in Figure 1 of the Lazarus reference. While Lazarus does teach morphine dosage for the patients varying between 30 mg every 12

hours up to greater than 90 mg every 12 hours, the "x" axis of Figure 1 corresponds to the total morphine sulfate (MSC) dosage range administered to the study patients and the "y" axis of Figure 1 corresponds to the average number of Senokot-S® administered with MSC daily doses (mg). Moreover, Lazarus expressly teaches, "Figure 1 represents the association between the total daily MSC dose in mg by the end of study and the total daily number of laxative tablets (in those 48 patients who took the tablets). There was a moderate relationship (r = 0.51) between dosage and senna/docusate consumption. On average, a daily dosage of 60 to 120 mg correlated with use of 3 SKS tablets daily (corresponding to 150 mg of docusate), greater than 120 to 180 mg MSC with 4 SKS tablets (corresponding to 200 mg of docusate), and greater than 180 mg MSC with 5 SKS tablets daily (corresponding to 250 mg of docusate)", on page 10, lines 5-12. Finally, while Applicant argues that the titration of the opioid dose separate from the dose of the laxative taught by Lazarus does not allow doubling or quadrupling of the opioid dose without doubling of the dose of the laxative contrary to the teachings of Lazarus, the Office notes that Applicant has not provided a clear and convincing reason or evidence that one of ordinary skill in the art would not be able to separately titrate the docusate dosage independent of the analgesic dosage to provide a single dosage form as instantly claimed by Applicant. Absent clear and convincing evidence to the contrary, the Office maintains the obviousness-rejection for the reasons set forth clearly in the previous Office action.

Thus, with Lazarus teaching a method of alleviating opioid-induced constipation comprising orally administering controlled-release morphine sulfate and 60-180 mg of

Senokot-S® (a combination laxative and stool softener containing senna and 50 mg of docusate, as evidenced by the teachings of drugs.com) except for wherein the pharmaceutical composition comprises the analgesic and the stool softener in a single dosage form, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the instantly claimed old and well-known ingredients taught by Lazarus to provide the instantly claimed inventions because Lazarus teaches that the simultaneous administration of morphine and docusate reduces the frequency of constipation in patients receiving pain control treatment by the administration of an opioid analgesic, on page 12, line 38 and page 13 in its entirety. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the form of the pharmaceutical composition and the method of oral administration of the two ingredients taught by Lazarus to provide the instantly claimed inventions because it would have been merely a matter of judicious selection to pick and choose the dosage form of the ingredients comprising the pharmaceutical composition given that the reference before him or her clearly teaches that the ingredients when simultaneously and orally administered provide the claim-designated functional effect for the prevention of constipation in humans receiving opioid analgesic treatment, especially since a single dose form would provide a convenient and easy dosage form for administration to patients in need of such therapeutic treatment; and, since Lazarus teaches, "Controlled-release oral morphine sulfate (MS Contin® Tablets*; MSC), represents an innovation over conventional immediate-release morphine and over the longer-acting narcotics

because of its convenient 12-hour dosing schedule and ease of administration combined with an efficacy and safety profile at least equal to that seen with conventional oral morphine", on page 3, lines 13-21.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-4, 8-24, 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V) in view of Kaiko et al. (D).

A method of preventing constipation during analgesic use comprising administration of a single solid dosage form comprising an opioid analgesic and at least about 50 mg of docusate is set forth immediately above, as obviated by the teachings of Lazarus. The obvious teachings of Lazarus teaches the instantly claimed invention except for wherein the single dose and the method for the oral administration thereof prevents constipation comprises the non-opioid analgesic acetaminophen; and wherein the opioid analgesic is codeine. However, it would have been obvious to one of ordinary skill in the art to modify the teachings of Lazarus by adding the instantly claimed acetaminophen to the method and the composition taught by Lazarus and to replace and/or add the opioid analgesic codeine to the composition taught by the obvious teachings of Lazarus because at the time the invention was made the addition of acetaminophen to a composition used in the treatment of patients receiving opioid

analgesic treatment was known for its beneficial effect, as evidenced by the teachings of Kaiko; and, Lazarus taught a conversion factor to determine the daily dose of opioids other than morphine or a combination thereof (*e.g.,* hydromorphone, methadone, levorphanol, oxymorphone, meperidine, oxycodone, codeine and pentazocine, *etc.*). Firstly, Kaiko teaches a pharmaceutical composition in solid dose form comprising an analgesic opioid, *e.g.,* codeine and hydrocodone, and acetaminophen (non-opioid analgesic) in a sustained release form for release of the ingredients over a period of time. In Column 11, line 49 to Column 12, line 3, Kaiko teaches that codeine, morphine, meperidine, fentanyl, hydromorphone, oxymorphone, oxycodone, hydrocodone, methadone, propoxyphene, pentazocine, levorphanol, and combinations thereof may be used in the making of his compositions. In Column 14, lines 27-49, Kaiko teaches that the amount of acetaminophen comprising the referenced composition is an amount of about 10 mg to about 2000 mg; and, in an amount of about 325 mg to about 1000 mg. In Column 34, lines 24-39, Kaiko further teaches orally administering hydrocodone and acetaminophen to patients under fasted conditions. Secondly, Lazarus teaches that a conversion factor can be conveniently used to determine the daily dose equivalent of one opioid for the equivalent dose of MSC. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the acetaminophen taught by Kaiko, and to substitute and/or add the MSC taught by Lazarus for codeine or any other equivalent opioid analgesic to provide the instantly claimed inventions because Kaiko teaches that it was old and well-known in the art at the time the invention was made that

acetaminophen can act synergistically with opioids and that such compositions comprising acetaminophen are also said to be subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression, in Column 14, lines 50-58; furthermore, in Column 34, lines 24-39, Kaiko teaches oral administrations of the reference compositions to provide the beneficial functional of this compositions to human subjects are effective under fasted conditions; and, Lazarus teaches that the simultaneous oral administration of morphine and docusate provides a method for the amelioration of constipation during analgesic use and that other opioid analgesics, such as the instantly claimed codeine is a functional equivalent of the referenced codeine (MSC). Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the instantly claimed inventions are no more than the combining of well-known ingredients and well-known methods for reducing the risk of or preventing adverse pharmacological side effects, such as constipation and drug addiction, in human subjects receiving analgesic therapy by the oral administration of opioids.

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations, as well, as the method steps for the administration thereof are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-4, 8-24 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V), and Kaiko et al. (B) in view of Colliopoulos (C) and Kais et al. (D).

The combined teachings of Lazarus and Kaiko are set forth above. The combined teachings of Lazarus and Kaiko teach the instantly claimed inventions except for wherein the stool softener is psyllium. However, it would have been obvious to one of ordinary skill in the art to add psyllium to the composition and method of use thereof taught by the combined teachings of Lazarus and Kaiko to provide the instantly claimed inventions because at the time the invention was made psyllium and docusate were known in the art for their beneficial functional effect, as evidenced by the teachings of Colliopoulos and Kais. Firstly, Colliopoulos teaches a dietary food composition comprising dioctyl sulfosuccinate (docusate) and psyllium having a laxative effect.

Secondly, Kais teaches a composition comprising encapsulated dioctyl sulfosuccinate (docusate) and psyllium having a laxative effect. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add and/or replace the stool softener used in the method of making the pharmaceutical composition and method of use thereof taught by the combined teachings of Lazarus and Kaiko to provide the instantly claimed pharmaceutical compositions and method of treatments because Colliopoulos teaches that the reference pharmaceutical compositions comprising psyllium may be dispersed in a palatable food product and orally administered to human subjects to provide a method of constipation; and, Kais teaches that the reference pharmaceutical compositions comprising docusate and psyllium may be used in the making of food products and orally administered to human subjects to provide a method of treating constipation. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the instantly claimed inventions are no more than the combining of well-

known ingredients and well-known methods for reducing the risk of or preventing adverse pharmacological side effects, such as constipation and drug addiction, in human subjects receiving analgesic therapy by the oral administration of opioids.

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations, as well, as the method steps for the administration thereof are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claim Objections

Claims 7 and 8 are objected to because of the following informalities: There is an apparent misspelling in line 2. Applicant may overcome the objection by replacing "phyllium" with psyllium. Appropriate correction is required.

No claims are allowed.

* Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Should you receive inquiries about the use of the Office's PAIR system, applicants may be referred to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood

MICHELE FLOOD
PRIMARY EXAMINER

MCF
March 21, 2005